09997.0087US01

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: FRANZ Michel
Appl. No.	: 10/789,174
Filed	: February 26, 2004
For	: STABILIZED PHARMACEUTICAL COMPOSITION COMPRISING AN EXTENDED RELEASE NOW-STEROIDAL ANTI-INFLAMMATORY AGENT AND AN IMMEDIATE RELEASE PROSTAGLANDIN
Examiner	: SILVERMAN, ERIC
Group Art Unit	: 1619

DECLARATION UNDER 37 C.F.R § 1.132

Mail Stop Amendment

Commissioner for Patents
P.O Box 1450
Alexandria, VA 22313-1450

Dear Sir:

1. This Declaration is being submitted to demonstrate that claimed invention unexpectedly provides a stability of pharmaceutical composition comprising an extended release non steroidal anti-inflammatory agent and an immediate release prostaglandin.
2. I am an inventor on the above- identified patent application and am familiar with the specification and prosecution history.
3. I have extensive experience in the field of the claimed invention as indicated in the attached Curriculum Vitae provided herewith as Exhibit A.

4. I have conducted Hydroxyl-Propyl-Methyl-cellusose (HPMC) a stability study during a period of 6 months. Capsules made of gelatine and made of hydroxyl-Propyl-Methyl-cellulose (HPMC) (containing extended release non-steroidal anti-inflammatory agents and an immediate release prostaglandin) were compared. The protocol of this study and the results of this study is presented in the enclosed Exhibit B.
5. This comparative data shows that a capsule made of Hydroxyl-Propyl-Methyl-cellulose present unexpectedly an increase stability compared to gelatine.
6. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or patent issuing therefrom.

Dated: October 26th 2006

By: _____
Michel Franz

EXHIBIT A

Michel FRANZ
avenue du Haut-Champ,52
B-1082 Brussels
michel.franz@skynet.be
Tel: 32(0)2 4654434 Cell Phone: 32(0)2 497 421363 Fax: 32(0)2 4694855

Profile

When graduated as a Pharmacist at Liège University (Belgium), I had two major areas of interest: Pharmacognosy and Pharmaceutical Technology.
I started with 2 years in Congo/Zaire at the University of Kinshasa (instead of military service) and came back in Belgium to begin a career in the Pharmaceutical Industry.
My first responsibilities were in manufacturing but I managed to move progressively to Pharmaceutical Development responsibilities.
I had the opportunity to work for several important pharmaceutical companies including Baxter, Laboratoires Thissen, UCB Pharma, Monsanto/ Searle, Lilly and Janssen Research Foundation, accumulating a broad experience in the early pharmaceutical development activities as well as the late stage technology transfer.
In parallel to my professional career, I was able to develop an interesting network in Belgium and abroad (Universities, Health and Business Authorities, Industrial Pharmacists, Excipients and Active Ingredients Suppliers, Machine Manufacturers) .

Personal informations

- Date of birth: 2 september 1945
- Nationality: belgian
- Education :
  University of Liège (1963-1968) : Pharmacist , Magna Cum Laude
  University of Brussels(1981-1982) : Solvay Business School Certificate
- Languages:
  French , mother language
  English , good spoken and written
  Dutch: good spoken

Miscellaneous

-Elected on the list of Industrial Pharmacists of the Belgian Health Ministry, n°598 (Qualified Person to release pharmaceutical products in the European Community)
-Visiting Professor and co-founder of the post -graduate teaching in Industrial Pharmacy organised by the 3 French speaking Universities in Belgium.
-Past Chairman and current member of the board of UPIP VAPI (Belgian Industrial Pharmacists Professional Association) and past national representative to the European Federation of sister associations.
-Active member in several professional and scientific other organisations
-Author or co-author of several publications and patents
-Good knowledge of the retail pharmacy and hospital pharmacy activities in Europe and Africa

Michel FRANZ CURRICULUM VITAE

Experience and Achievements

From beginning of 1999- today- **FRANPHARMA sprl**

- ***Consultant*** in Pharmaceutical Product Development
- Missions in Belgium, France, The Netherlands, North Africa and the US.

1996 to January 1999-**Janssen Research Foundation** (Beerse)

- *Senior Project Manager*
- I had to coordinate pharmaceutical product development activities on projects being worked out intra the company or in collaboration with Drug Delivery Companies

1993-1996-**Lilly Development Centre** (Mont-Saint-Guibert)

- *Scientific Advisor*
- The function included the following responsabilities:
  Advice to the Pharmaceutical Development activities
  Contacts to identify opportunities in the field of Drug Delivery Systems
  Improvement of the network with Universities and other official bodies in Belgium and in Europe

1978-1993-**Continental Pharma / Monsanto/ Searle** (Louvain-la--Neuve)

- Management positions in (bio)pharmaceutical development, R&D
  Last: *Senior Director*, European Pharmaceutical Development
- The function included the following responsabilities (analytical & technological):
  Pre-formulation, formulation for New Chemical Entities
  Design of new formulations for existing products
  Manufacturing and Quality Control of dosage forms used during clinical trials
  Packaging of clinical supplies for international studies (shipment to 40 countries)
  Technology Transfert to manufacturing sites in France, UK, Puerto Rico , Germany
  Participation to the selection of manufacturing equipment and Plant design for Manufacturing and Control
  Preparation of the CMC section of regulatory affairs documents for worldwide applications
- The biggest project we finalised is Arthrotec, a patented core tablet (US 5,015,481) with cumulated sales well over 1 billion $!

1974-1978- **UCB Pharma** (Brussels and Braine-l'Alleud)

- *Pharmaceutical Technology Manager*
- I have (re)formulated several key products, including Nootropil tablets
- The job gave me the opportunity to work in both Manufacturing & Control and R & D environments.

1972-1974- **Laboratoires Thissen** (Therabel Group) Uccle

- *Manufacturing Supervisor*
- In a short period of time I was able to gather a good experience as the company is working as a contract lab. The diversified nature of the products was giving me a prime chance to solve formulation issues .

1971-1973- **Baxter-Travenol** (Lessines)

- *Quality Control Supervisor*
- I was exposed early in my career to the concept of the GMPs, in a state of the art plant built to produce Large Volume Parenterals and other hospital products.

1969-1971- **University of Kinshasa** (Zaire)

- *Lecturer at the School of Pharmacy*
- In addition to teaching I was doing research on endemic plants (Strychnos and Dioscoreas).

Exhibit B

A stability study has been performed during a period of 6 months. Capsules made of gelatine or hydroxypropylcellulose (HPMC) containing Extended Release Diclofenac Sodium pellets and one Immediate Release Misoprostol mini-tablet were compared.

The attention was focused on the stability of Misoprostol as it is a very sensitive compound. The analytical methodology to assay Misoprostol and the impurities was based on the monograph recently published in the European Pharmacopeia (monograph 1731, January 2006).

The moisture of the Misoprostol mini-tablets was designed to be high to accelerate the degradation of Misoprostol and to facilitate the evidence of the possible difference between the 2 types of capsules. The mini-tablets moisture results were : 7;44% in the gelatine capsules and at 7.98% in the HPMC capsules.

Both types of capsules were packaged in aluminium-aluminium blisters which are offering an excellent protection against atmospheric agents during the storage.

We report the results obtained on packaged capsules stored at 30°C/65% Relative Humidity and 40°C/75% Relative Humidity.

The comparison of the data indicates clearly that the use of HPMC capsules offers a clear advantage over the gelatine capsules for the stability of the prostaglandin.

Condition : + 30°C/65% RH

Timepoint (months)	Misoprostol Content (mg)	Misoprostol Content (% of label claim)	Total Epimers	Misoprostol A	Misoprostol B	Total impurities
Gelules gelatine						
0	0,193	96,7	0,68	0,14	nd	0,82
1	0,197	98,3	0,93	0,46	0,04	1,45
3	0,191	95,7	1,19	0,87	0,15	2,21
6	0,188	94	1,85	1,90	0,62	4,37
Gelules HPMC						
0	0,191	95,5	0,77	0,12	nd	0,89
1	0,197	98,6	1,04	0,39	0,01	1,44
3	0,195	97,4	1,34	0,66	0,03	2,03
6	0,191	95,7	1,01	1,20	0,08	2,29

Condition : + 40°C/75% RH

Timepoint (months)	Misoprostol Content (mg)	Misoprostol Content (% of label claim)	Total Epimers	Misoprostol A	Misoprostol B	Total impurities
Gelules gelatine						
0	0,193	96,7	0,68	0,14	nd	0,82
1	0,192	95,8	1,63	2,12	0,66	4,41
3	0,175	87,6	2,43	4,07	2,37	8,87
6	0,151	75,5	4,33	6,94	6,03	17,30
Gelules HPMC						
0	0,191	95,5	0,77	0,12	nd	0,89
1	0,197	98,7	1,18	1,63	0,09	2,90
3	0,186	93,1	1,69	3,53	0,23	5,45
6	0,174	87,1	1,87	7,66	0,62	10,14

Impurities are expressed in % of the theoretical amount of Misoprostol.

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DECLARATION UNDER 37 C.F.R § 1.132

Mail Stop Amendment

Commissioner for Patents
P.O Box 1450
Alexandria, VA 22313-1450

Dear Sir:

1. I am an expert in pharmacy and I am familiar with the specification and prosecution history of the above- identified patent application.
2. I have extensive experience in the field of the claimed invention as indicated in the attached Curriculum Vitae provided herewith as Exhibit A.

Appl. No. : 10/789,174
Filed : February 26, 2004

3. I have performed an analysis of the stability study conducted and provided by the inventor Michel Franz which was enclosed to his declaration of October 26, 2006.
4. In this study capsules made of gelatin and made of hydroxyl-Propyl-Methyl- cellulose (HPMC) and containing Misoprostol were compared
5. In this comparative study capsules made of hydroxyl-Propyl-Methyl- cellulose present unexpectedly an increased stability compared to gelatin capsules. This declaration mentions that this study was focused upon the stability of Misoprostol as it is a very sensitive compound.
6. The other active compound present in the claim composition is an extended release non-steroidal anti-inflammatory agent who is known to be stable. Delayed release non-steroidal anti-inflammatory agent is also known to be a stable compound. Therefore, as an expert, I can confirm that the provided stability study is sufficient to demonstrate the advantages of HPMC capsules compared to gelatin capsules and I can confirm that the presence or the absence of another compound (non- steroidal anti-inflammatory agent such as diclophenac present in any type of formulation (extended release formulation or delayed release formulation)) would not affect the provided results described in Dr Franz declaration.
7. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or patent issuing therefrom.

Dated: 10th January 2007

By: 
Karim Amighi

CURRICULUM VITAE

Personal information

Karim AMIGHI
Born on December 28, 1962 in Tehran, Iran.

Private address: Brusselsesteenweg 43, 3080 Tervuren - Belgium.

Business address: Free University of Brussels (ULB),
Pharmacy Institute, Campus de la Plaine, CP 207,
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E-mail: kamighi@ulb.ac.be

Education

- Degree in Pharmaceutical Sciences (1987), Free University of Brussels (ULB).

- Degree in Industrial Pharmacy (1988), Free University of Brussels (ULB).

- Ph.D. in Pharmaceutical Sciences (1996), Free University of Brussels (ULB).

Thesis: Etude de l'influence des paramètres de formulation, de fabrication et de conservation sur les propriétés de formes orales multi-unitaires à libération prolongée, enrobées à l'aide des dispersions aqueuses de polymères acryliques.
Advisor: Prof. André Moës

Experience

Oct 2001-	Professor of Pharmaceutical Technology, Pharmacy Institute, Free University of Brussels.
Oct 1997-Sep 2001	Associate Professor of Pharmaceutical Technology, Pharmacy Institute, Free University of Brussels.
Oct 1989-Sept 1997	Research Assistant in Pharmaceutical Technology, Pharmacy Institute, Free University of Brussels.

Teaching Area

- Pharmaceutics and Biopharmaceutics

- Pharmaceutical Technology.

- Drug Formulation and Preformulation.

- Dermopharmacy and Cosmetology.

- Hospital Pharmacy.

Current Research Interests

- **Oral controlled and targeted drug delivery systems**
  - ✓ Thermoplastic granulation – pelletization.
  - ✓ Colonic drug delivery systems.
  - ✓ Gastro-retentive dosage forms (Floating tablets and pellets).
  - ✓ Bioadhesive nanoparticles systems (enzymes).

- **Synthesis and development of new excipients / carriers**
  - ✓ Thermosenitive copolymers (Poly (N-isopropylacrylamide PNIPAAm).
  - ✓ Epichlorohydrin cross-linked pectin.
  - ✓ Bioadhesive nanoparticles.

- **Oral bioavailability enhancement of drugs (BCS II and IV)**
  - ✓ Crystalline nanoparticles for solubility and dissolution rate enhancement.

- **Pulmonary drug delivery systems**
  - → Powder for inhalation (DPIs): Anti asthmatics, antibiotics and anti cancer drugs.
  - → New fillers and/or carriers for inhalation (SLP).
  - ✓ Increased tolerance.
  - ✓ Increased drug deposition.
  - ✓ Controlled-drug release.

- **Parenteral and implantable drug delivery systems**
  - ✓ Nanoparticulate parenteral suspensions and emulsions for administration of drugs (anti cancer).
  - ✓ Biodegradable implantable gel system based on GMO for the treatment of chronic osteomyelitis (gentamicin).

Publications

- **45 peer reviewed publications** including the *Journal of Controlled Release, International Journal of Pharmaceutics, European Journal of Pharmaceutics and Biopharmaceutics, European Polymer Journal and Pharmaceutical Research.*

- **50 presentations** in scientific meetings.

Selected representative publications

1. K. Amighi and A.J. Moës, Evaluation of thermal and film forming properties of acrylic polymer aqueous dispersion blends : application to the formulation of sustained-release film coated theophylline pellets, Drug Dev. Ind. Pharm., 21 (20), 2355-2369, 1995.

2. D.B. Beten, K. Amighi and A.J. Moës, Preparation of Controlled-Release Coevaporates of Dipyridamole by loading neutral Pellets in a Fluidized-Bed Coating System, Pharm. Res., 12 (9), 1269-1272, 1995.

3. K. Amighi and A.J. Moës, Influence of curing conditions on the drug release rate from Eudragit NE30D coated sustained-release theophylline pellets, STP Pharma Sciences, 7 (2), 25-31 (1997).

4. K. Amighi, J. Timmermans, J. Puigdevall, E. Baltes and A.J. Moës, Peroral sustained-release film-coated pellets as a means to overcome physicochemical and biological drug-related problems: I. In vitro development and evaluation, Drug Dev. Ind. Pharm., 24 (6), 509-515 (1998).

5. F. Eeckman, A.J. Moës and K. Amighi, Conception of oral controlled-drug delivery systems based on the use of thermoresponsive polymers, Int. J. Pharm., 241(1), 135-125 (2002).

6. R. Semdé, A.J. Moës, M.J. Devleeschouwer and K. Amighi, Synthesis and enzymatic degradation of epichlorohydrin cross-linked pectins, Drug Dev. Ind. Pharm., 29(2), 203-213 (2003).

7. J. Hamdani, A.J. Moës and K. Amighi, Development and evaluation of controlled-release lipidic pellets obtained by the melt granulation, Int. J. Pharm., 245, 167-177 (2002).

8. F. Eeckman, A. Moës and K. Amighi, Surfactant induced drug delivery concept based on the use of thermosensitive polymers, J. Control. Release, 88, 105-116 (2003).

9. H. Malonne, F. Eeckman, D. Fontaine, A. Otto, L. Devos, A. Moës, J. Fontaine and K. Amighi, Preparation of poly(N-isopropylacrylamide) copolymers and preliminary assessment of their acute and subacute toxicity in mice. Eur. J. Pharm. Biopharm. 61, 188-194 (2005).

10. J. Hecq, M. Deleers, D. Fanara, H. Vranckx and K. Amighi, Preparation and characterization of crystalline nanoparticules for solubility and dissolution rate enhancement of nifedipine, Int. J. Pharm, 299, 167-177 (2005).

11. T. Sebti and K. Amighi, Preparation and in vitro evaluation of new lipidic carriers and fillers for inhalation, Eur. J. Pharm. Biopharm. 63(1), 51-58 (2006).

12. G. Pilcer, T. Sebti and K. Amighi, Formulation and characterisation of lipid-coated tobramycin particles for dry powder inhalation, Pharm. Res. 23(5) 931-940 (2006).

13. J. Goole, J. Hamdani, F. Vanderbist and K. Amighi, In vitro and in vivo evaluation in human volunteers of floating riboflavin minitablets, J. Drug Deliv. Sc. Technol. 16(5), 351-356 (2006).

14. T. Sebti, G. Pilcer, B. Van Gansbeke, S. Goldman, A. Michils, F. Vanderbist and K. Amighi, Pharmacoscintigraphic evaluation of lipid dry powder budesonide formulations for inhalation, Eur. J. Pharm. Biopharm., 64(1), 26-32 (2006).

15. J. Hecq, G. Nollevaux, M. Deleers, D. Fanara, H. Vranckx, G. Dandrifosse, O. Peulen and K. Amighi, In vivo pharmacokinetic evaluation and in vitro transport studies across Caco-2/HT29-5M21 cultures and co-cultures of nifedipine nanocrystals, In Press, J. Drug Del. Sc. Technol. (2006).

16. J. Goole, F. Vanderbist and K. Amighi, Development and evaluation of new multiple-unit levodopa sustained-release floating dosage forms, In Press, Int. J. Pharm (2006).

Ph.D. Thesis under the supervision of K. Amighi

1. Benameur Hassan (2003), Développement, optimisation et caractérisation d'une pro-drogue lipophile de la dexaméthasone sous forme liposomale.
2. F. Eeckman (2003), Développement et évaluation d'un nouveau concept de libération de substances actives, basé sur l'utilisation de polymères thermosensibles.
3. J. Hamdani (2005), Développement de formes orales divisées à libération prolongée par la technique de la pelletisation thermoplastique
4. Th. Sebti (2006), Développement et évaluation de formulations lipidiques à poudre sèche pour inhalation.
5. J. Hecq (2006), Development, characterization and evaluation of crystalline nanoparticles for enhancing the solubility, the dissolution rate and the oral bioavailability of poorly water-soluble drugs.

Scientific awards

K. Amighi received the price of 5th section of Belgian Academy of Medicine for his works concerning the new applications of polymers in pharmaceutical technology (June 2002).

Professional Societies

Karim Amighi is a member of numerous scientific organizations including The Controlled Release Society, Belgium Society of Pharmaceutical Sciences, Belgian Royal Society of Chemistry, APGI (Association de Pharmacie Galénique Industrielle) and APV (Arbeitsgemeinschaft für Pharmazeutische Verfahrenstechnik).

Scientific collaborations

1. Prof. S. Goldman, Dr. D. Blocklet, B. Van Gansbeke, Service de Médecine Nucléaire, Faculté de Médecine, Hôpital Erasme, ULB.
2. Prof. P. De Vuyst, Dr. A. Michils, Dr. Christiane Knoop, Service de Pneumologie Faculté de Médecine, Hôpital Erasme, ULB.
3. Prof. L. Delattre, Dr. B. Evrard, Lab. de Technologie Pharmaceutique, ULg.
4. Prof. M. Van Damme, Dr. R. Kiss, Laboratoire de Toxicologie, Institut de Pharmacie, ULB.
5. Prof. J.T. Fell, Department of Pharmaceutical Technology, University of Manchester;
6. Prof. J. Dubois, Laboratoire de Chimie Bioanalytique, de Toxicologie et de Chimie physique appliquée, Institut de Pharmacie, ULB.
7. Prof. L. Angenot, Dr. M. Tits, Lab. de Pharmacognosie, ULg.
8. Prof. G. Dandrifosse – Dr O. Peulen, Service de Biochimie et Physiologie générales de l'ULg ;
9. Prof. M-P. Delplancke-Olgetree, Laboratoire de Chimie Industrielle, Faculté des Sciences Appliquées – Chimie, ULB ;
10. Prof. I. Guissou et Dr. R. Semdé, Université de Ouagadougou, Burkina Faso (Projets de coopération au développement (conventions de recherche C.U.D., International Fondation for Science IFS).
11. Prof. Ph. Thonart, CWBI – Gembloux – ULg.
12. Pôle d'excellence en recherche agro-industrielle en Hainaut « Agro-Food Valley ».

Industrial collaborations

UCB ; SMB-Galéphar ; Unibioscreen ; Chemo Iberica ; Liconsa ; Dow Corning ; Rhöm Pharma Polymers ; Gattefossé ; GSK Biologicals ; Fédéra ; Thérabel Research. ; Noveon.